HYPERSPLENISM *

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It has been the usual experience in medicine, that as scientific knowledge about disease grows, the number of etiologic entities within any given clinical syndrome increases, with a corresponding expansion and diversity of specific therapy. Tonight, we shall be discussing the much rarer opposite phenomenon, viz., a mechanism, hypersplenism, which appears to be common to a wide range of clinically and etiologically separate syndromes, for all of which, nevertheless, one therapeutic procedure, splenectomy, is now advised. It seems not to depend upon whether the symptoms are chronic or acute, whether they reflect recurrent and prolonged invalidism, or present as a rapidly fulminating emergency, which may threaten the survival of the patient in a matter of hours,—the results of splenectomy are equally dramatic.

John H. King of Johns Hopkins, reporting in August 1914 on "Studies in the Pathology of the Spleen,"[1] which he had just completed with Eppinger in Vienna, observed that "many diseases of the blood are associated with striking changes in the morphology of the spleen. Often, indeed, the gross change in this organ is the dominating feature of the clinical picture . . . yet little progress has been made in the attempt to correlate changes in the spleen with clinical symptoms. That this organ has important functions can hardly be questioned. There is, for example, considerable evidence to show that the spleen may have a marked influence on hemolysis. It is but a step then to assume that there may exist for the spleen conditions associated with an hyperactivity of some of its functions, let us say the function of influencing hemolysis. To such a condition the term "hypersplenism" may be applied . . . If it can be shown that important clinical symptoms consistently point to a hyperfunction of the spleen, and that these symptoms disappear, or are strikingly mitigated, when the spleen is removed from

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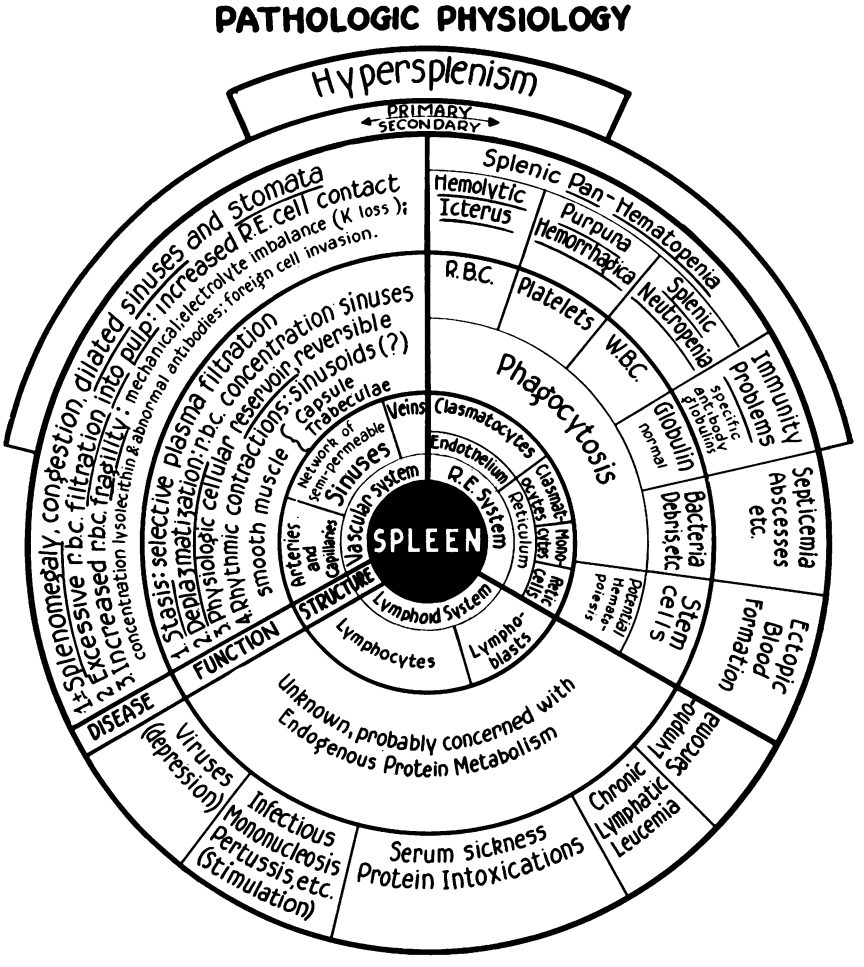

Figure 1—Pathologic physiology of the spleen

the body, an important step will have been taken toward defining the changes in function of the spleen." This is the first use of the term "hypersplenism," which we have found in the medical literature. A clearer forecast or a surer prophecy of the hypersplenic states which have since been recognized, and of their therapeutic response to splenectomy, could hardly be imagined.

The once enigmatic, physiologically non-essential spleen has now fully proved itself to be an exceedingly unstable, and, therefore, path-

ologically important organ. Whether it has inherited, as a Mendelian dominant gene factor, the *primary* capacity to withhold and destroy excessive numbers of circulating red blood cells (congenital hemolytic icterus),[2] or platelets (thrombocytopenic purpura),[3] or granulocytes (splenic neutropenia),[4] or destroys all three indiscriminately at the same time (pan-hematopenia),[5]—*or*, whether the spleen acquires these traits *secondarily*, through becoming involved in one or other of a number of unrelated constitutional diseases,[5]—when the hypersplenic mechanism has been established by the appropriate diagnostic procedures now clinically available, quick and sure action by the surgeon of the team is mandatory, and is usually effective.

As seen histologically, the spleen is not unique (Fig. 1), presenting simply a reduplication of the cellular elements common to many other tissues and organs in the body. The lymph follicles are identical with those found in all lymph nodes. The reticulo-endothelial phagocytes, though greater in quantity, are not unlike in quality those found in liver, bone marrow, mesenteric lymph nodes, and the diffuse connective tissues. No specific secreting cells which would appear to be potentially capable of producing an internal secretion have ever been described. The specificity of the "thrombocytopen" of Trolland and Lee,[6] and of splenin I and II of Ungar[7] has as yet been difficult of confirmation in other laboratories, including our own. The experimental extirpation of the spleen in many animal species, and the accumulated experience of emergency splenectomy for traumatic rupture of the normal human spleen,[8,9] have effectively confirmed these morphological findings and interpretations, and have firmly established the fact that this organ is not essential to the maintenance of normal health and longevity at any age in any species.

The Spleen and its Vascular Sinuses

We must turn then to anatomical considerations for at least a part of the explanation of the unique relationship which this organ seems to bear to the human pathological states, with which we are concerned. Unlike lymph nodes and liver, the spleen possesses a smooth-muscle-reinforced capsule and penetrating intra-parenchymal trabeculae, which provide an intrinsic mechanism for the rhythmic physiologic contraction and relaxation of this organ. A sharp contraction of the spleen occurs after voluntary muscular exercise, after hemorrhage and after

psychic (adrenalin) stimulation.[10] The diagnostician may take advantage of this neuro-muscular mechanism to obtain a non-surgical "biopsy" of the potentially mobilizable splenic cell content at any desired moment by securing peripheral blood cell and blood volume studies before and after the injection of adrenalin.[11] A biphasic curve of total cell and differential fluctuations will reflect within 60 to 90 minutes the initial contraction and subsequent compensatory hyper-relaxation of the spleen before it returns to its pre-adrenalin tonal equilibrium. By preceding such a study with sodium pentobarbital, it is possible to induce an initial relaxation of the muscular tone of the spleen with an increase in its sequestration of the blood elements reflected by a transitory reduction of as many as 37 per cent of the circulating erythrocyte population.[12]

This ability of the spleen to change its volume has been known for a long time, at least since 1723, when Stukeley[13] observed the spleen to enlarge in size as he injected blood into the jugular vein of dogs. The direct relationship, which has been repeatedly observed to exist between changes in spleen volume and circulating cell volume has inevitably focused attention sharply upon the nature and character of the circulation, which must govern this reservoir activity,—and as a direct corollary, the extent and effect of such storage on the involved blood cells. Increasingly ingenious methods have been developed for studying this most richly vascularized organ in the body. Proceeding from the older fixed tissue techniques, Knisely[14] perfected the procedures for direct observation by transillumination of the living intact spleen in a number of animal species, and concluded, contrary to Mollier[15] and Mall,[16] et al, that the circulation everywhere within the splenic pathway is closed. Large intercommunicating sinuses, with afferent and efferent physiologic sphincters, connect arterioles and veins, permitting periodic closure when distended with blood, in which phase the plasma passes through the sinus wall by filtration, leaving the red cells concentrated and completely shut off from the active circulation for as long as 10 hours at a time. MacKenzie, Whipple and Wintersteiner,[17] however, in attempting to repeat Knisely's observations on the spleen in the living animal, failed to confirm his interpretations. They believe the chief concentration of erythrocytes is in the splenic pulp rather than in the sinuses, the parenchyma receiving its complement of red cells through fenestrations in the club-like ampulae of Malpighi at

the ends of the capillaries. The red cells appeared to be slowed down or "blocked" from time to time by aggregations of white corpuscles, which subsequently gave way to permit re-entry of the erythrocytes through openings in the walls of the veins, synchronous with and mediated by the rhythmic contractions of the spleen which occurred as originally described by Barcroft.

During the spring of 1947, Sven Erik Björkman published a very complete monograph on the Splenic Circulation[18] from Prof. Faraeus' laboratory at the University of Upsala. He critically analyzes the investigations of the past 100 years, adding his own experimental animal and human studies in an attempt to extend and clarify the earlier observations. Using gelatin to induce erythrocyte rouleaux formation, and saponin to produce less elastic spherocytes in rabbits, Björkman found that the pulp cords contained very few and the sinuses most of the red cells, whereas in the untreated controls there was a more equitable distribution between pulp and sinuses. He interpreted this to suggest that small changes in the size and shape of suspended particles, or aggregations of particles are important to their vascular filterability. By injecting intravenously starch granules measuring 1 to 5 *mu* in diameter, and identifying their intra-vs extra-vascular position, it was possible to further measure the approximate size of the suspected stomata under various conditions. Whereas under physiologic conditions 95 per cent of the starch granules 1 *mu* or less in diameter were found to have passed into the pulp cords, while 80 per cent of the granules 5 *mu* were still in the sinuses, after inducing an acute splenic tumor by experimental streptococcus infection or by intoxication with an hemolytic agent, only 50 per cent of the larger starch granules remained within the sinuses. An enlargement of the vascular stomata, under these pathologic circumstances, was hypothesized. Transferring his observations to selected human autopsy material, Björkman believes he has evidence to support the concept of an identical human splenic vascular mechanism, in which in acute splenic tumor in man there is sinus dilatation with an accelerated intercourse for both plasma and corpuscular elements between sinuses and pulp cords, via broadened and distended stomata. Conversely, in chronic cardiac decompensation and hepatic cirrhosis, Bjorkman describes a pathological modification of the splenic sinus wall structure, as reported earlier by Matsui,[19] with an increasing number of longitudinal anastomoses between the normally

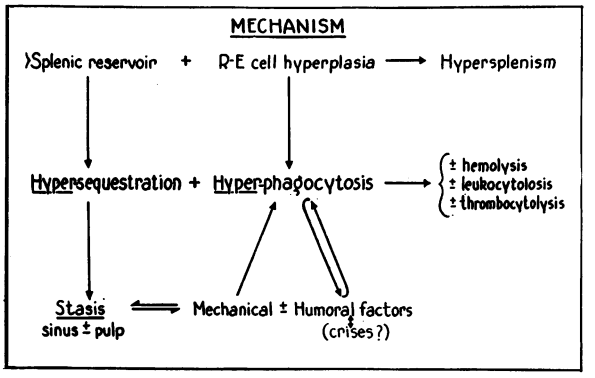

Figure 2—Mechanism of hypersplenic states, theoretical considerations.

annular fibrils in the sinus and venous walls, which would tend toward a compensatory preservation of the tightness of the sinus fllter in resistance to a mounting portal hypertension.

Watzka[20] and Snook[21] have separated the various species in which the splenic circulation has been studied into two major groups: 1) those with poor sinus development, viz., cat, dog, cow, horse, sheep, swine, hedgehog, mole, ermine, weasel, and mice, and 2) those rich in these vascular structures: man, ape, rabbit, guinea pig, rat and squirrel. This variability in species and in pathologic splenic state may well explain the variations in emphasis in the study of an organ where it now seems certain that both sinuses and pulp cords are important circulatory reciprocals.

Thus it would seem fair to accept as our current working hypothesis (Fig. 2) the concept that the human spleen has a semi-open circulation, controlled by a filter mesh mechanism in the sinus wall, which by heredity or under many diverse pathologic conditions may be altered, either in the direction of greater or lesser selective permeability to the cellular elements of the blood. This circulatory mechanism, unique as compared with all other organs and tissues, operates to separate the cells from the plasma, and thus to concentrate in the spleen, both within and without the sinuses, in varying degree and quantity, blood cells of various types and quality.[22] The more disturbed the circulatory equilibrium, the more profound and prolonged the stasis, the more does the

spleen seem to lack discrimination and to withhold normal as well as fragile, senile and damaged elements.

The hypersplenic sequence of events my well include: abnormal stasis within splenic sinuses and/or pulp[23,24] calling for a compensatory increase in delivery of marrow elements; deplasmatization with increased mechanical intercellular friction;[25] loss of erythrocyte potassium with other electrolyte disequilibria, leading to increased fragility;[26] pathologic concentration of lysolecithin and lysolecithin-like, spherocyte-inducing biochemicals normally produced in physiological amounts by the R-E cells,[27] with hemolytic blocking[28,29]or other polyhemagglutinin antibodies[30] theoretically derivable from the R-E cells, exceptional opportunity for immediate contact-phagocytosis by R-E elements;—all in all an ideal environment for the establishment of a vicious cycle of cell withholding and cell destruction capable of acceleration or deceleration, depending upon a variety of factors. The dramatic immediacy of the termination of a true hemoclastic crisis at the operating table, at the moment of ligation of the splenic pedicle, strongly incriminates this inherent, chemico-mechanical splenic mechanism.[2]

The Role of the Bone Marrow

Turning now from the spleen per se, what role, if any, does the bone marrow play in the human hypersplenic states? The microcytic, spherocytic, hyper-fragility of the erythocytes associated with the hemolytic syndromes has been attributed to an inherited, inherent marrow defect.[31] Dameshek[32] and others have proved that all of these qualities are readily acquired by the definitive erythrocyte after marrow delivery, and it is difficult, if not impossible, to demonstrate these characteristics in the reticulocytes obtained directly from the marrow in these patients. The reports[33,34] of a normal survival time for transfused erythrocytes from normal donors in patients with acute hemolytic crises, in contradistinction to a relatively shorter survival time for their own marow product,—and that such transfusion support should be given routinely,—have not been confirmed in our experience. On the contrary, we believe the administration of borrowed red cells in acute hemolytic crises is both unnecessary (Fig. 3) and extremely dangerous. Attributing the excessive hemolysis of freshly transfused red blood cells in these patients to inaccurate isoagglutin or Rh typing, though this danger is always a possibility, can hardly account we believe, for

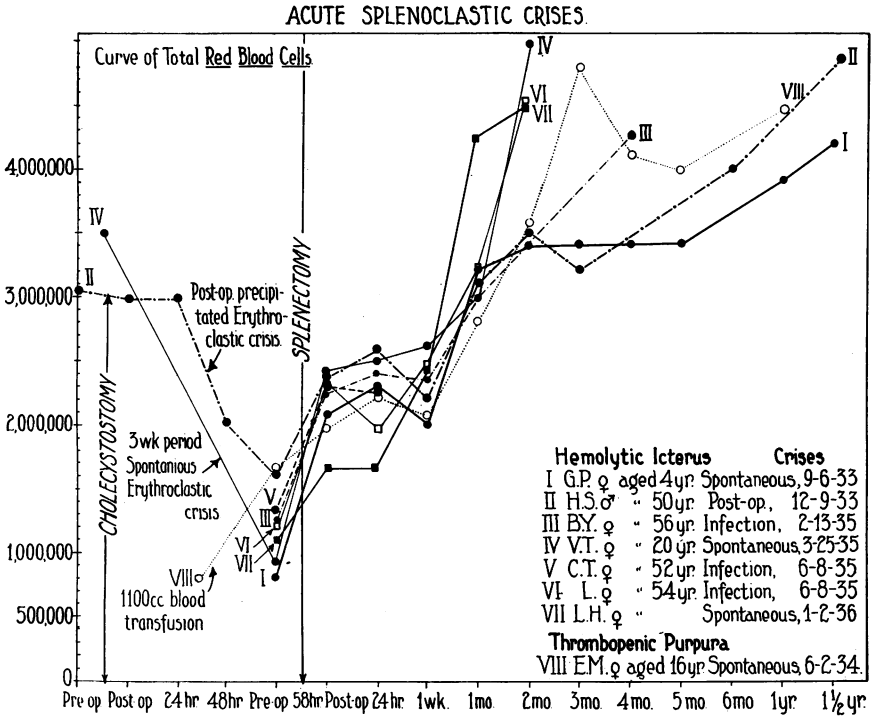

Figure 3—Three patients showing spontaneous erythroclastic crises, three with crises precipitated by infections, and one following surgery other than splenectomy, all responded similarly to emergency splenectomy irrespective of age or sex. The speed of red cell recovery was essentially identical in these patients with congenital hemolytic icterus and in patient VIII with a comparable anemia secondary to acute thrombocytopenic purpura.

all of the fatal reactions reported in the medical literature. Dameshek and Bloom[34] also find this phenomenon to vary from case to case. In Case 6 of their recently reported series, the red cell survival time, studied by the Ashby technique, was diminished during crisis, and became normal only after splenectomy. These authors have failed to find instances of sudden acute pan-marrow aplasia, as reported recently by Owren[35] in congenital hemolytic icterus, nor have we encountered this particular mechanism in the true acute hypersplenic crises, which have come under our observation in recent years. We have seen acute marrow aplasia, reflected by pancytopenia in the peripheral blood, but in each of these instances the differential diagnosis was established, first with reference to the exclusion of any hypersplenic factor, and then in terms

of the type of specific infection or chemical or drug idiosyncrasy, individually or collectively responsible. It is entirely possible for hypersplenism and marrow aplasia to occur coincidently in the same patient, or for aplasia to be precipitated in a patient with a previously demonstrated hypersplenic diathesis by any one of the many agents potentially operable in any other susceptible individual; but we believe the mechanisms should not, and need not, be confused. If, and when, epidemic disease does attack several members in a family with an inherited hyperinstability of the spleen, it may more readily invoke a sudden transitory hypersplenic episode, but any direct bone marrow damage is an additional complication adding greatly to the hazards, in contrast with the excellent prognosis when the hypersplenic mechanism alone is involved.

Two other more probable marrow mechanisms, which may be mediated by or through the pathologic spleen, have been seriously considered and proposed, viz., cell maturation arrest and/or delivery inhibition or "block." Krumbhaar[36] many years ago showed a sustained supra-normal rise in thrombocytes and erythrocytes in dogs post-splenectomy, suggesting some regulatory or inhibitory function affecting the level of circulating blood cells. Dameshek and associates have favored this interpretation of the cellular response which follows splenectomy in congenital hemolytic icterus, from studies of the fixed films and sections of marrow, and after finding "no evidence of erythrophagocytosis in studies of the splenic histology," also in fixed sections. Our own observations of fixed tissues in these cases have in every instance been supplemented by studies of the living marrow and spleen tissues, using supravital stains. Under these more favorable circumstances, it is quite easy to see, for example, in addition to those megakaryocytes rounded up in the "resting" phase, others in the same microscopic field with fragmenting cytoplasm in active platelet formation, even when a profound thrombocytopenia exists in the circulating blood. Likewise in aspirations or direct scrapings of living splenic tissue from any and all of the hypersplenic states, the highly phagocytic clasmatocytes or R-E cells are characteristically present in excessive numbers,—at times 10 to 12 per oil immersion field, from a spleen weighing perhaps 2000 grams,—differing only in the specificity of their phagocytized cell content, which in turn is directly related to the type and specificity of splenic reservoir cell sequestration, and is reciprocal to the circulating cytopenia. Specifically, in primary splenic neutropenia (Fig. 4), the bone

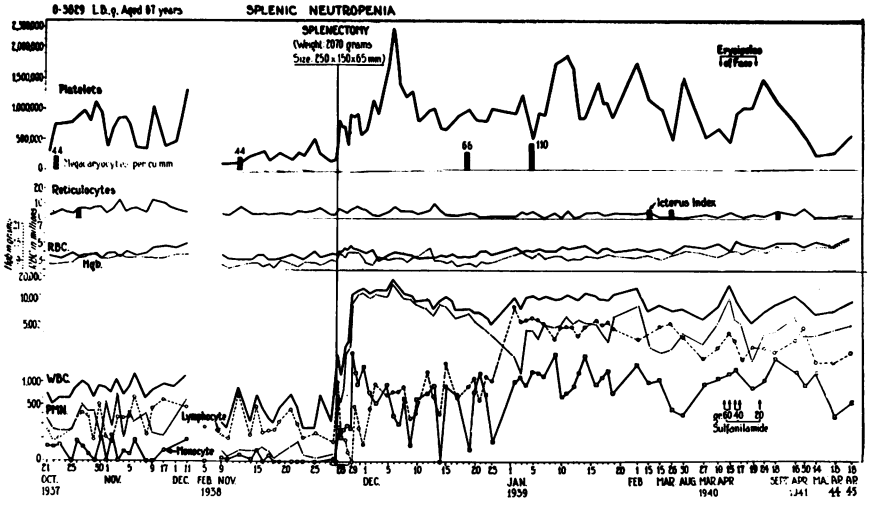

Figure 4—Primary splenic neutropenia progressing over a 12-month period to panhematopenia due to an extension of the same hypersplenic mechanism. Splenectomy completely and permanently restored the cellular and clinical equilibrium (11 years).

marrow is hyperplastic for neutrophilic myelocytes obviously maturing normally with delivery of motile band forms into the circulation at an accelerated rate; the sinuses and parenchyma in the greatly enlarged spleen have their usual complement of sequestered mature erythrocytes almost entirely replaced by these same granulocytes which may be found both without and specifically within the highly phagocytic R-E cells; the capillary circulation meantime may show as few as 25 granulocytes per cu. mm.; adrenalin contraction of the spleen may be expected to raise this circulating increment of granulocytes transitorially to 10,000 or more per cu. mm., in which case, splenectomy is almost certain to permanently correct the dyscrasia.

It will be clear from the foregoing discussion, that the bone marrow mechanism, which we have thought to be most frequently invoked in those pathologic states included in our definition of "hypersplenism," comprises the following interrelationships: maximum compensatory hyperplasia, with normal maturation and accelerated delivery of the specific marrow element or elements involved, which elements, nevertheless, remain in dangerously low negative balance in the circulating blood, due to an increasingly complete and absolute withdrawal of

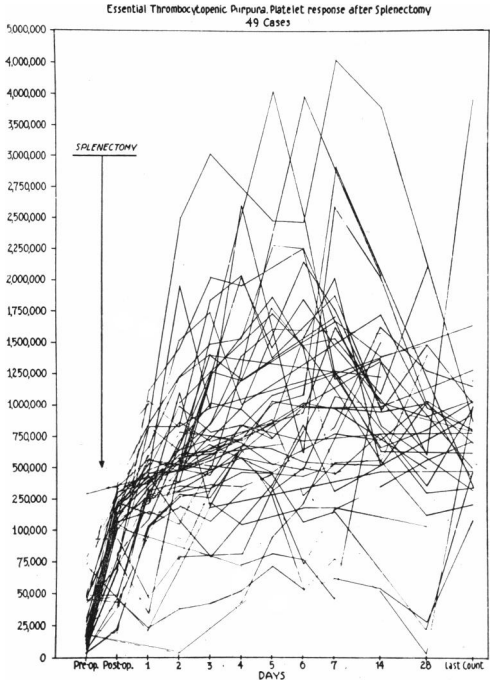

Figure 5—The peripheral thrombocyte response to splenectomy in 49 consecutive cases of thrombocytopenic purpura.

these essential blood cells by the spleen.

Final proof of the hyper-sequestration versus the marrow inhibitory role of the spleen in any given instance would seem to rest on the results of a carefully controlled study of the blood entering and leaving the spleen before and after adrenalin, during surgical exploration in an active phase of such cellular disequilibrium. During the past year we have been making such observations in appropriately selected patients with the surgical coöperation of Dr. Robert Zollinger. These data will be presented in detail elsewhere. Suffice it to say, here, that this direct evidence effectively eliminates any bone marrow inadequacy of cell maturation and delivery as major factors, at least in those patients so studied, at the same time placing the full pathologic responsibility on the splenic tissue in situ.

Reference to Fig. 5 on which are graphed 49 consecutive cases of primary splenic thrombocytopenic purpura, will reveal the immediacy,

the uniformity and the magnitude of the increase in circulating platelets which occurred at the operating table on the day of surgery, in all but five patients. Splenic artery and vein studies in a representative sampling of this series confirmed the bone marrow and adrenalin test interpretations of active platelet delivery, the splenic artery in one patient, for example, carrying 450,000 platelets per cu. mm. to the spleen, while the vein leaving the spleen contained only 17,000 platelets per cu. mm. Five minutes after adrenalin injection into the splenic artery, the splenic vein contained more than 400,000 platelets. This could be interpreted either as a closing of the sinus-pulp reservoirs temporarily by the contraction of the spleen creating an arterio-venous shunt, or it could represent a reservoir release of temporarily trapped platelets; in either interpretation the integrity and activity of the bone marrow is attested. In the five cases which showed a much slower and more gradual post-operative increase in the circulating platelets, the evidence might be interpreted as a gradual recovery of inhibited megakaryocytes reciprocal to the gradual elimination of some humoral agent produced by the spleen. Lacking as yet objective reproducible evidence of a circulating "thrombocytopen," this explanation must be left "sub judice" for the present.

In primary uncomplicated hypersplenism, then, as we have seen and interpreted these syndromes in our Clinic, the bone marrow plays only a reciprocal physiologic role, compensating, eventually maximally, in response to an excessive peripheral demand for blood cells, which demand fluctuates from time to time with the unpredictability of an inherently unstable and pathologicaly hyper-reactive spleen. The net increment of blood cells at any one moment in the circulating blood is always the resultant of the balance between supply and demand. Whenever any disturbance in this cellular equilibrium, so essential to health, occurs, either the supply must be increased or the demand reduced, promptly. In the hypersplenic states we must eliminate an excessive pathologic demand, more or less wholly created by the spleen, and which may or may not be compensable by the marrow. If and when the marrow becomes inadequate, the spleen must be promptly sacrificed, or the survival of the individual will be gravely threatened. Once freed of all splenic tissue, we have never found such individuals to show any further inadequacy or incompetence of the marrow for any and all demands through many years.

Primary Hypersplenism

Primary hypersplenism we define as an hyper-instability of the spleen, sometimes inherited as a Mendelian dominant gene factor, as in congenital hemolytic icterus, and, at other times, when direct human inheritance is difficult to establish, perhaps as a recessive character of infrequent expressivity. In such circumstances "spontaneous" hypersplenic episodes may occur, unrelated to any demonstrable internal or external environmental cause, such physiologic stresses as a normal pregnancy, and minor infections and traumata, frequently and repeatedly precipitate more or less severe hypersplenic exacerbations or "crises" in "susceptible" patients. For these reasons, whenever a true hypersplenism is recognized, prophylactic splenectomy must be seriously considered. Elective splenectomy is much to be preferred to emergency splenectomy for obvious reasons. Irrespective, however, of the degree of cytopenia or of the acuteness of the clinical syndrome, the response to splenectomy is equally prompt and sustained.[2]

Furthermore, it is seldom that we encounter a "pure" hemolytic or an unadulterated thrombocytopenic or neutropenic syndrome. The predominant clinical picture may be anemia, with or without jaundice, or purpura, or Ludwig's angina and infection, but any one of these symptom complexes will be found more often than not to have a subclinical if not clinical cytopenia involving one or more of the other elements of marrow origin. At different stages in the clinical course of the same patient, differing degrees of pan-hematocytopenia may be observed (Fig. 4) reflecting the variable withholding idiosyncracy of the pathologic spleen for the cells coming to it.

One of our patients, a 14 year old girl when first seen in consultation, had a history of more or less continuous, severe pan-hematocytopenia since birth. Every laboratory examination showed every organic function to be normal, except for a pan-marrow hyperplasia of normally maturing cells in normal relative proportions, and for the adrenalin test which was interpreted as reflecting an unequivocal splenic pan-cellular hypersequestration. Splenectomy was followed by a prompt peripheral hematologic re-equilibration, and by a complete clinical metamorphosis from chronic invalidism to normal health and physical activity. The surgery was consummated in October 1943. No other pathology has developed in the intervening 5½ years (Fig. 6).

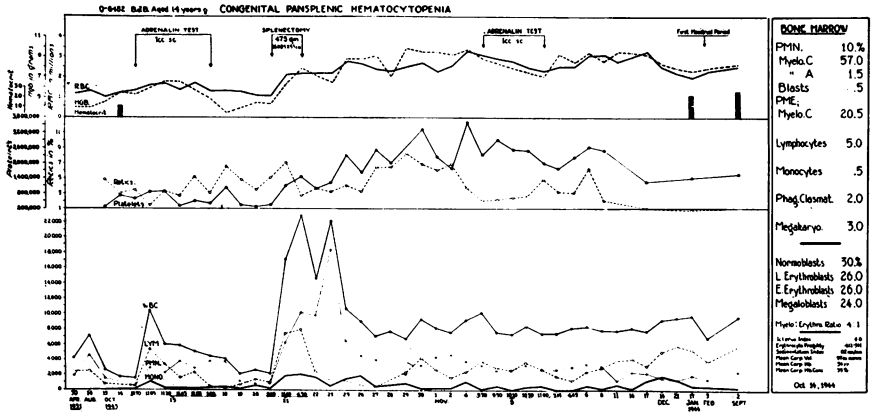

Figure 6—Congenital splenic panhematopenia from birth to 14 years; originally misdiagnosed as due to an hypoplastic bone marrow. Splenectomy has been followed by a sustained recovery clinically and hematologically.

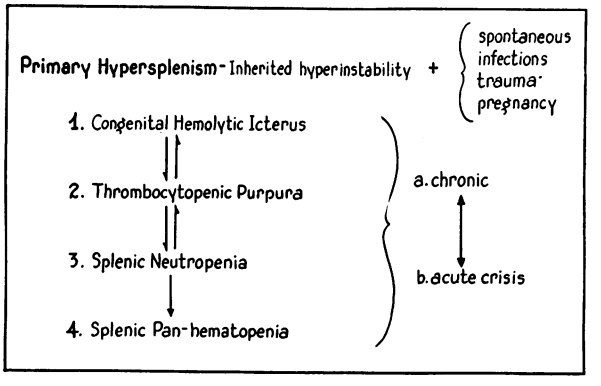

Figure 7—Primary hypersplenism.

Those clinical entities recognized under the general category of "primary hypersplenism" and their interrelationships as we have found them to occur in our series of case studies are shown in the graph (Fig. 7).

Hypersplenism Secondary to Other Diseases

During the course of a number of diseases the spleen may become secondarily involved (Table I). In a certain proportion of these cases

TABLE I—SECONDARY HYPERSPLENISM

Secondary or Acquired Hypersplenism—normal instability + { unusual / pathologic / stress }

Non specific—miscellaneous constitutional diseases.

1. Congestive
2. Infiltrative
3. Hemoblastic (the leukemias)
4. Inflammatory
5. Neoplastic
6. Myelofibrosis with splenomegaly, with or without hematopoiesis

TABLE II—326 SPLENECTOMIES
1932 - 1949

HYPERSPLENISM TOTAL	(82%)	270	
Primary		(65%)	176
Secondary		(35%)	94
MISCELLANEOUS TOTAL	(9.5%)	30	
Hypoplastic Anemia (relative splenic factor)			14
Polycythemia Rubra Vera			2
Sickle Cell Anemia			2
Lymphatic Leukemia			9
Myelogenous Leukemia			3
Erythroblastic Leukemia			1
NORMAL SPLEEN CONTROLS	(8.5%)	26	
Traumatic rupture (All Columbus Hospitals)			22
Secondary to other surgery (exposure)			4
TOTAL			326

there develops a syndrome identical with one or other of those already described as primary hypersplenism, in which both specific splenic hypersequestration and compensatory bone marrow hyperplasia may be demonstrated, though there is no familial history of such a trait. Hemoclastic crises may occur which threaten the survival of the individual quite independently of his basic disease. Under such circumstances splenectomy is indicated and may, and sometimes must, be undertaken,

TABLE III—270 HYPERSPLENIC CASES

1932 - 1949

270 SPLENECTOMIES FOR HYPERSPLENISM

PRIMARY

Congenital Hemolytic Icterus	75	Recurrences	
Thrombocytopenic Purpura	77	a. Accessory Spleens	4
Splenic Neutropenia	13	b. Generalized R.E. Cell Hyperphagocytosis	5
Splenic Pan Hematopenia	11		

SECONDARY

a. *Congestive Splenomegaly*		d. *Inflammatory Splenomegalies*	
Banti's Syndrome	42	Tuberculosis	3
Felty's Syndrome	6	Syphilis	1
Acquired Hemolytic Icterus	16	Moniliasis	1
b. *Infiltrative Splenomegaly*		Boeck's Sarcoid	2
Gaucher's Disease	4	Hodgkin's Syndrome	5
Xanthomatosis	1		
c. *Hemoblastic Splenomegaly*		e. *Neoplastic Splenomegaly*	
Lymphatic Leukemia	4	Retothelio Sarcoma	1
Myelogenous Leukemia	2	Hemangioma	2
Monocytic Leukemia	1	Multiple Myeloma	1

f. *Myelofibrosis* with fibrous splenomegaly without myeloid metaplasia 2
(With myeloid metaplasia 4 cases, no splenectomy)

with the more remote prognosis, however, correspondingly guarded. In no instance have we noted any exacerbation of the underlying disease process because of the splenic surgery, and most often the improvement which follows the re-establishment of a more nearly normal blood cell equilibrium is directly beneficial in the further management of the original disease.

In our series of 326 splenectomies (Table II), 82 per cent were diagnosed as hypersplenism, and of the 270 splenectomies for hypersplenism, 65 per cent have been classified as without otherwise demonstrable disease, therefore as primary, and 35 per cent as secondary to some other obvious basic pathology. Because of the frequency with which the spleen, when involved in other pathologic processes (Table III), has been observed to assume an aggressive activity against the blood cells entering its sinuses, it now seems appropriate to consider this

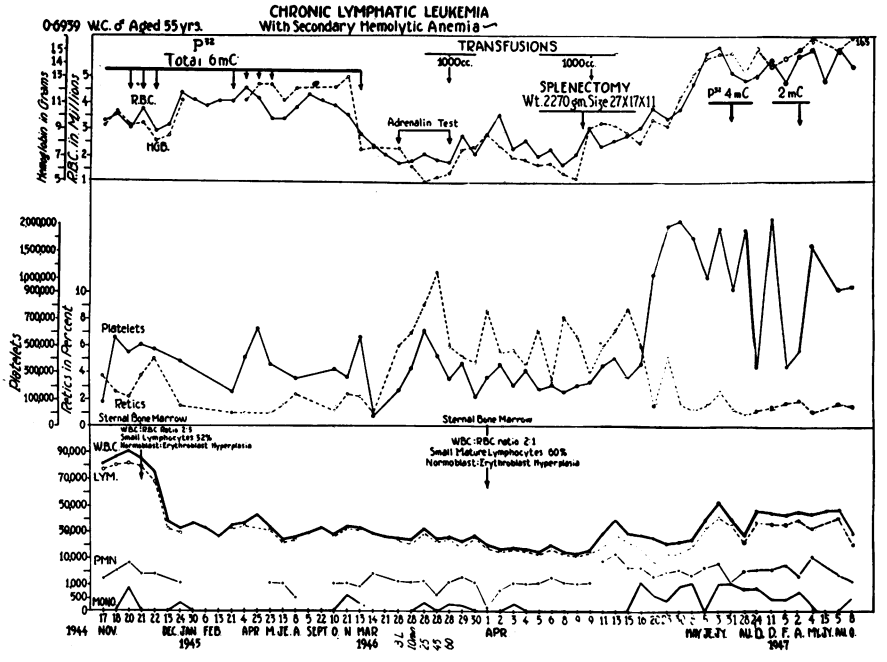

Figure 8—Acute erythroclastic crisis during the course of chronic lymphatic leukemia.

organ as possessing a considerable degree of "normal instability," not unlike, qualitatively, the inherited "abnormal hyperinstability" of the primary syndromes. The unique structure of this organ, as required for its physiologic functions (Fig. 1), lends itself admirably to circulatory disturbances associated with parenchymal cellular invasion, and the large complement of phagocytic cells already there await only the time and opportunity, which stasis and engorgement inevitably provide.

Three examples only will be cited from this series. During the course of chronic lymphatic leukemia (Fig. 8) in a white male, aged 57, who had been under satisfactory control with radioactive phosphorus for several years, there developed an acute hemolytic crisis. Appropriate laboratory studies ruled out both radiation damage and lymphocytic myelophthesia of the marrow as contributing factors while revealing a marked compensatory normoblastic hyperplasia, and splenic hyper-erythro-sequestration. Splenectomy was advised, after transfusions had proven ineffective, and was followed by an immediate cessation of

erythrocyte destruction. The underlying leukemia has continued to respond to small infrequent doses of radioactive P-32 to the present time. There have been no further hemolytic episodes.

A white male patient aged 39 years presented with all of the clinical and hematologic findings characteristic of acute primary thrombocytopenic purpura, including typical compensatory megakaryocytosis in the bone marrow without other demonstrable pathology. Splenectomy was followed by an immediate and sustained thrombocytosis, and the prompt disappearance of all purpuric manifestations. Histologic study of the spleen, however, revealed a well developed Hodgkin's granuloma, though neither liver nor lymph nodes, grossly or microscopically, showed any sign of this disease at this time. One year later the primary disease proved terminal, despite intensive therapy, but there was no recurrence of the purpura which had threatened survival from hemorrhage a year earlier.

A young woman, aged 20 years whose sister eight years previously had undergone splenectomy for Gaucher's disease, suddenly developed a rapidly enlarging abdominal tumor associated with profound peripheral blood changes. The total circulating leukocytes were only 1300 per cu. mm., the red cells 3,180,000, and the platelets 111,440. An adrenalin test decreased the tumor size and increased temporarily the circulating level of all of the normal blood elements. A sternal marrow study showed compensatory pan-marrow hyperplasia of all essential elements. An occasional Gaucher cell was found which served to establish the diagnosis. Similar studies of the sister's marrow revealed Gaucher cells in limited number, insufficient, however, to have influenced adversely the normal circulating blood cell equilibrium during the years since her earlier splenectomy. A 5000 gram spleen was removed without complications, followed immediately by the re-establishment of a normal sustained circulating level of all blood cells. Marriage and a normal pregnancy have been accomplished without untoward incident meantime.

Reference to Table III will show the range of diseases thus far encountered in our clinic, which have shown at some time during their clinical course, an involvement of the spleen sufficient to precipitate a more or less acute hypersplenic crisis, for which complication, surgery has been deemed imperative for survival. In none of these individuals have we been able by history or direct examination of blood relatives

to establish an hereditary factor. It is for this reason that we are hypothesizing a so-called "normal instability" of the spleen in its reservoir function for any or all of the blood cells, which due to the unique circulatory mechanism of this organ, plus its high content of R-E cell phagocytes, permits of ready imbalance in the circulating levels of the blood elements, which normally pass through or remain only temporarily in its parenchyma.

Acute Hemoclastic Crises

As already stated, the hypersplenic mechanism, whether primary or secondary, may precipitate some of the most acute critical acellular clinical syndromes which the physician and surgeon are called upon to diagnose and treat. Uncontrollable hemorrhage, a profound hemolytic anemia, or sudden sepsis may dominate the clinical picture. An immediate and thoroughly critical blood and bone marrow study is the first essential in the differential diagnosis. There may be insufficient time for a confirmatory adrenalin test or other extensive laboratory investigations. The theoretical considerations, which may explain this sudden negative balance between bone marrow supply and peripheral demand for any or all of the essential blood elements, we believe involve both the mechanical and/or humoral factors inherent in the vascular and cellular organization of the spleen (See Figs. 1 and 2). Whether the blood platelets, the erythrocytes, the granulocytes, or any possible combination of these elements are found to be deficient in the blood stream, the marrow must be hyperplastic for their precursors, without evidence of maturation arrest or qualitative abnormalities, if and when a true uncomplicated hypersplenism is the sole cause. In such syndromes, splenectomy is followed by a prompt and complete cellular re-equilibration, as reflected in the seven patients with acute erythroclastic crises in congenital hemolytic icterus and in the one patient with acute thrombocytopenic purpura (Fig 3). The curve of recovery of the red blood cells in each of these eight cases follows the same general pattern and timing, though the anemia in the first seven was hemolytic in origin and in the eighth it was secondary to hemorrhage. All of the factors which govern the specificity and degree of cellular deficit from patient to patient, and in the same patient from time to time are still unrevealed, but the evidence to date tends to incriminate the spleen rather than the bone marrow.

Relative Hypersplenism

In certain patients, who have experienced permanent marrow damage from industrial toxins, but in whom progressive mesenchymal destruction has been halted by removal from the environment, the normal physiologic reservoir function of the spleen may be sufficient to prevent cellular recompensation. After a sufficient period of supportive therapy, if the marrow hyperplasia continues to prove inadequate for the demand, splenectomy should be considered and will permit at times in selected patients, a more nearly normal circulating increment of cells.

Traumatic Rupture of the Spleen

Control studies have been made in those healthy individuals who have suffered sudden traumatic rupture of the spleen requiring emergency splenectomy for intra-abdominal hemorrhage and shock. In a survey of some 22 such individuals, the hematologic equilibria and the health and clinical resistance to ordinary infections have remained unimpaired (Table II). The normal human spleen is apparently not essential to life or health. Conversely the pathologic human spleen may threaten both health and longevity.

Post-Splenectomy Failures and Recurrences

The importance of differential diagnosis in the establishment of a true hypersplenic syndrome cannot be overemphasized. Obviously other mechanisms may simulate superficially these specific splenic entities, the most common of which involve the bone marrow, upon the integrity of which the body is dependent for its continuing resupply of new cells throughout life. Progressive marrow hypoplasia on the basis of any nutritional deficiency or toxic etiology, intrinsic or extrinsic in origin, must be recognized and corrected per se at the earliest possible moment. Myelofibrosis and osteopetrosis may be accompanied by compensating extramedullary hematopoietic splenomegaly, which when associated with a precipitated hypersplenic episode may strongly suggest splenectomy. Under such circumstances a positive adrenalin test will usually reflect a sharp increase in circulating nucleated red blood cells and myelocytes, but on occasion such evidence of local splenic hematopoiesis is lacking. If repeated bone marrow aspirations fail to reveal active blood cell regeneration from any and

all sites (sternum, spinous process, iliac crest, ribs), it may be necessary to aspirate the splenic parenchyma directly, or secure a tissue biopsy, before a judgment may be reached as to the relative importance of the productive versus the destructive roles of the spleen in any particular instance. In six such patients only two showed a predominant hyperdestructive activity by the enlarged spleen with negligible hematopoietic function. Both of these patients benefited by splenectomy. A tightly packed avascular leukemic marrow may simulate at times, an hypoplastic state, and with a sub-leukemic peripheral absolute leukopenia, anemia and thrombocytopenia, may lead to an erroneous interpretation of the splenomegaly.

In only a very few instances, fortunately, have we encountered a generalized R-E cell hyperplasia and hyperphagocytosis, in our non-bone marrow cytopenic states, so that liver, lymph nodes, marrow and connective tissues participated sufficiently to render clinically ineffective the removal of the excessively large increment of phagocytes in the spleen. Until proven otherwise, therefore, the principal pathologic focus in these patients may be assumed to be the spleen.

Accessory Spleens

An initial characteristic post-splenectomy remission may at times be followed after a few months or even after several years by a recurrence of the same or an entirely different type of hypersplenic syndrome. Experience has taught us to be immediately suspicious of some remaining accessory splenic tissue when this occurs. The marrow is again studied immediately and must show specific hyperplasia of the deficient circulating elements without maturation arrest or abnormal qualitative alterations. Accessory spleens or implanted splenotic fragments from a traumatically ruptured or surgically torn spleen may become hypertrophied and functionally pathologic. Re-exploration is definitely indicated when the laboratory data confirm a recurrent mechanism of hypersequestration and destruction. Thorotrast visualization will frequently assist the surgeon in locating the embryonic splenic rests in remote areas, including the retroperitoneal gutter.

Our first patient to be subjected to splenectomy during an acute erythroblastic crisis in congenital hemolytic jaundice experienced a dramatic recovery hematologically and clinically. which lasted 4½ years (Fig. 9). At the end of this period the same type of hemolytic,

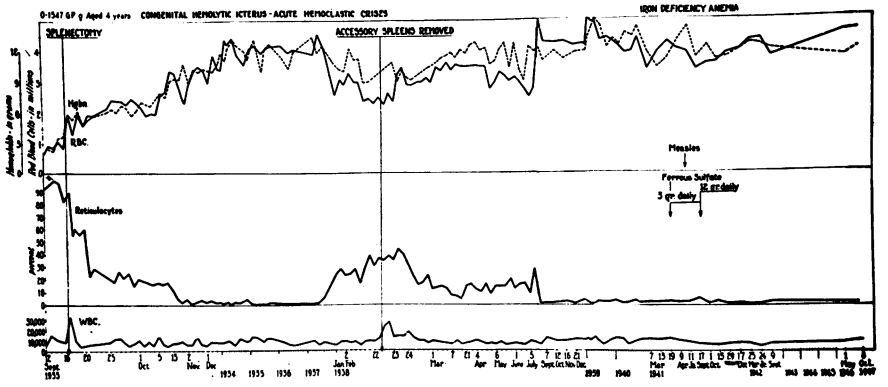

Figure 9—Recurrent hemolytic icterus caused by accessory splenic tissue. Recovery followed removal of 3 small accessory spleens.

icteric anemia re-appeared with reticulocytosis and compensatory normoblastic marrow hyperplasia identical with the first episode. When all medical measures had failed, a surgical re-exploration was undertaken and three small accessory spleens, totaling not over 5 gms. by weight in all, were found and removed. Mesenteric nodes and a biopsy of the liver were obtained at the same time from normal appearing tissues, and histologic examination confirmed the normalcy of these organs. The accessory splenic tissues, however, contained excessive numbers of highly phagocytic clasmatocytes loaded with red blood cells, and a second remission followed their removal. This has continued to the present time 11 years later,—16 years after the first operation.

The fact that few carefully studied hypersplenic episodes represent a pure single cell strain sequestration has been previously emphasized, together with the observation that the same individual patient may at different times show different cell-type deficits, reflected by entirely different clinical syndromes—all of which tends to center attention upon splenic tissue, its unique circulatory system, functionally designed for storing normal cells and salvaging damaged and senile blood elements,—rather than upon the organ of their origin, the bone marrow. This double danger of differential splenic selectivity was demonstrated in one of our patients in two dramatic episodes separated in time by 18 months. A young man 16 years of age (Fig.10) developed without previous warning, an acute erythroclastic crisis, typical of congenital

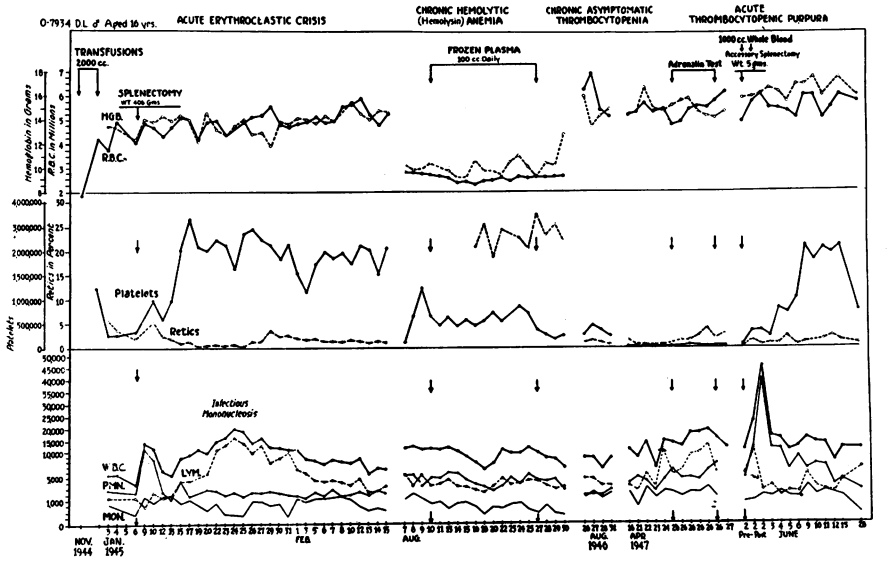

Figure 10—Primary congenital hemolytic icterus, acute crisis, relieved promptly by removal of the spleen. Eighteen months later an acute thrombocytopenic purpura without anemia was promptly relieved by the removal of an accessory 5 gm. spleen.

hemolytic jaundice. Complete recovery followed splenectomy. Some eighteen months later he developed, equally suddenly, an acute spontaneous fulminant thrombocytopenic purpura without any evidence of hemolytic anemia. Bone marrow studies confirmed the presence of increased numbers of actively multiplying and fragmenting megakaryocytes apparently responding to an increased peripheral demand for platelets. All other laboratory data excluded any other possible contributing mechanism. Following preoperative blood transfusions, a re-exploration was made and a 5 gram accessory spleen was discovered at the upper pole of the left kidney retroperitoneally. Upon its removal there was an immediate cessation of oozing in the operative field and the studies of the blood showed a coincident re-appearance of platelets in large numbers. There has been no further cellular disequilibrium in this lad to date.

Reference is made in this general connection to the patient already cited, who first presented with a relatively pure primary splenic neutropenia, only to develop within twelve months a splenic panhemato-

penia involving all of the circulating blood elements, with complete and permanent pan-cellular re-equilibration following splenectomy, continuing to date 11 years (Fig. 4).

Failure of complete and permanent restoration of health following splenectomy in true hypersplenic states will only be encountered in those individuals in whom the hypersplenism is secondary to progressive constitutional disease involving other organs. The ultimate outcome in such patients obviously will depend upon the effectiveness of the therapy for the primary disease. Nevertheless, when the predominant clinical syndrome in such patients can be proven to reflect an hypersplenic mechanism, this complication may and must be considered on its own merits. The best clinical judgment in our clinic has been more frequently than not to eliminate the focus of disease in the spleen together with the accompanying and resultant hypersplenic cellular imbalance, both of which threaten the health and survival of the patient. Only if a substantial cellular contribution is actually being made by a compensating, ectopic hematopoietic focus in the spleen, will the patient be less well off without rather than with his spleen.

Contraindications to Splenectomy

The contraindications to splenectomy may be sharply defined and clearly stated: 1) any acute or chronic bone marrow damage; 2) myelofibrosis, and 3) osteopetrosis in which the splenomegaly usually reflects ectopic hematopoiesis; 4) pan-myelophthesia; 5) ectopic splenic hematopoiesis plus secondary hypersplenism.

Summary and Conclusions

The spleen has inherited a unique anatomical structure, in which the relationship between smooth muscle capsule, pulp, and large fenestrated sinuses makes for an ideal physiologic reservoir for blood cell storage. The selective concentration of the stored elements of the blood, through the mechanism of deplasmatized stasis,—which in turn probably hastens unfavorable qualitative alterations in these cells,—when combined with an abundance of naturally occurring R-E cells, provide a basis for an apparent inherent homeostatic cellular instability in acquired, and an inherited hyper-instability in primary hypersplenism. A sub-acute, low-grade cellular disequilibrium may lead in one patient to chronic invalidism; in another, the same mechanism may result in a

vicious cycle, in which an acutely developing negative cellular balance will threaten survival. The resulting anemia, leukopenia or thrombocytopenia, which may be highly selective and specific, or in any combination and degree, underlie and govern the wide range of symptoms and signs which characterize these syndromes. Therefore, when the bone marrow is eliminated as a contributing factor, and a basic splenic mechanism is established, prompt removal of the spleen and all accessory splenic tissue provides the only assurance of a complete and lasting hematologic and clinical remission.

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